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MULTIPLE CASES IN REITER'S SYNDROME*

BY

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Multiple cases of Reiter's syndrome, whether following dysentery or apparently transmitted by sexual intercourse, have been occasionally reported in the literature. They fall into two groups: familial cases (Koster and Jansen, 1946; Glauner, 1947; Paronen, 1948; Trier, 1950; Morton, 1958; Csonka, 1958) and non-familial cases (Kristjansen, 1930; Durel and Siboulet, 1954; Csonka, 1959). The recorded incidence of multiple cases of both groups is higher in the post dysenteric syndrome than in the venereal syndrome.

The present study analyses 332 consecutive patients with venereal Reiter's syndrome for the occurrence and type of multiple cases.

Material and Methods

The patients, 318 men and 14 women, were seen at the venereal diseases Clinics of the Central Middlesex Hospital and St. Mary's Hospital, London. 302 were of European stock and 30 were Negroes. The average age at onset was 29 years (range 15 to 72). The patients were carefully questioned for similar cases in their own families and in their sexual contacts. When the history suggested that such related cases existed every effort was made to see the affected individuals personally. In two cases this was not possible but a full medical report was obtained from their doctors. In addition, the history of rheumatoid arthritis and other rheumatic disorders in parents, brothers, sisters, and children was recorded and compared with the incidence of the same disorder in the families of 400 patients with uncomplicated non-gonococcal urethritis (NGU); these latter patients, who were matched for age, race, and social background and had attended the same clinics during the period of study, served as controls.

Results

Two pairs of brothers, two husbands and their wives, a man and his girl friend, and two sexual contacts of one girl developed Reiter's syndrome and are briefly described. All these patients were of European stock.

(1) *First pair of brothers* The brothers, aged 31 and 34 years respectively, developed classical Reiter's syndrome each with NGU, acute polyarthritis especially affecting the lower limbs, and bilateral conjunctivitis. The attacks began within 9 months of each other; both were severe and both lasted for more than three months. One brother was married, the other single; they lived in different parts of England and had not met for over a year before the onset of their illnesses. A common sexual source was denied. Their mother and maternal aunt had rheumatoid arthritis.

(2) *Second pair of brothers* One brother, a single man aged 25, developed NGU after sexual contact in Sweden and this was followed by conjunctivitis, polyarthritis, sacroiliitis, extensive keratoderma blennorrhagica, and stomatitis. The attack lasted with some fluctuations for about a year. The other brother, aged 27, had developed Reiter's syndrome 6 months earlier in Dublin at the time of his marriage. His illness was remarkably similar to that of his brother in the type, distribution, and severity of the lesions, which remained active for 8 to 9 months. The family history showed that their mother had suffered from rheumatic fever with mitral stenosis, the father had undefined "rheumatism", and the paternal aunt had rheumatoid arthritis.

(3) *First married couple* The wife had had symptoms resembling those of rheumatoid arthritis for several years since she was aged 25, interspersed with three attacks of classical Reiter's syndrome with non-gonococcal cervicitis, polyarthritis, and conjunctivitis. Repeated tests for the rheumatoid factor were negative and the electrocardiogram was

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normal. Her mother was believed to have suffered from rheumatoid arthritis. The husband developed NGU, polyarthritis, and conjunctivitis 2 years after the onset of arthritis in his wife; the attack had an acute onset, was of moderate severity and lasted for 3 months. He has been symptom-free for the past $2\frac{1}{2}$ years. The family history of the husband was negative for rheumatic diseases. His wife continues to have low-grade arthritis involving mainly the knee joints and recently had an episode of non-gonococcal salpingitis. Extramarital intercourse was denied by both.

(4) *Second married couple* In 1954, the wife, then aged 28, had an acute attack of polyarthritis of the peripheral joints with fever and urticaria. A diagnosis of rheumatic fever was made but later abandoned as the course of the illness did not support the diagnosis. The only positive laboratory findings were a raised antistreptolysin titre and a raised erythrocyte sedimentation rate. The attack subsided after a few months. In 1961 she had a similar attack during pregnancy. Further acute attacks occurred in 1965 and 1968, when there was also non-gonococcal cervicitis, and stomatitis. Repeated tests for the rheumatoid factor and for L.E.-cells were negative. In 1967 her husband, aged 43, developed for the first time typical Reiter's syndrome with NGU, polyarthritis, plantar fasciitis, and conjunctivitis followed by iritis and superficial keratitis. Extramarital intercourse was strongly denied by both patients. The family history of the wife was negative for rheumatic diseases but the husband's brother suffers from ankylosing spondylitis.

(5) *Married man and his girl friend* These were both in-patients of the same hospital within 2 months of each other, both with Reiter's syndrome, but at that time their relationship was unknown to us and only came to light later after a chance remark by the patient's wife. The man had his first attack of Reiter's syndrome at the age of 18 and since then had had three well-defined episodes. He developed his third attack in July, 1964, and his girl friend of that period had a similar attack 2 months later (Fig. 1). Both attacks were severe, but whilst the man continued to have arthralgia and painful feet for a considerable period after the acute attack was over, the girl recovered completely within 3 months and has remained well during the observation period of 2 years during which time she married and had a child. The man's wife was examined and found to have *Trichomonas vaginalis* vaginitis but no other abnormalities; the girl's future husband was asymptomatic. The family history in both patients was negative for rheumatic diseases. It may be of interest that the girl had well-marked keratoderma blennorrhagica of the feet which is considered unusual in women with Reiter's syndrome (Fig. 2).

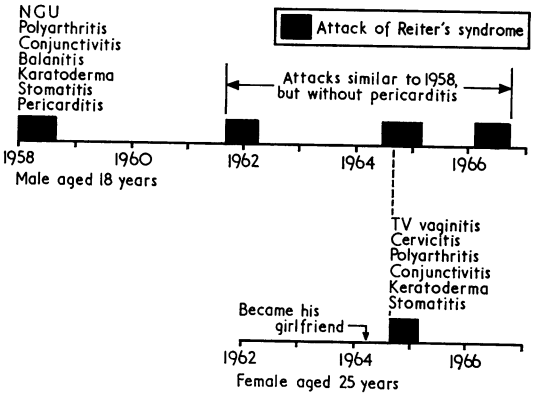

FIG. 1.—Reiter's syndrome in a man and his female sexual partner.

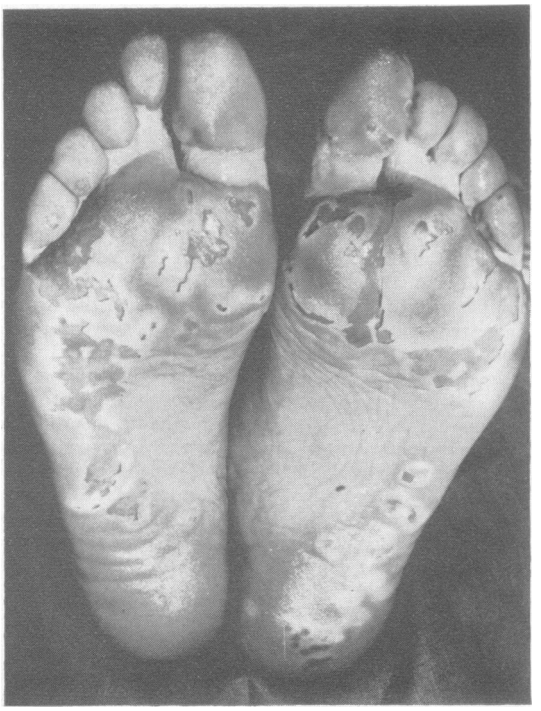

FIG. 2.—Keratoderma blennorrhagica in a female patient with Reiter's syndrome.

(6) *Two unrelated young men and a girl friend common to both* They were seen at one of the clinics in the same week. One of the men had NGU and polyarthritis, mostly of the joints of the lower limbs, and the other had NGU and marked bilateral conjunctivitis. Both had had sexual relations with the same girl 10–14 days before the onset of their symptoms. The girl was found to have non-gonococcal leucorrhoea and cervicitis but no signs of Reiter's syndrome. No complete family history for rheumatic diseases was available as the patients had lost contact with some of their relatives.

Family History for Rheumatoid Arthritis

A positive history was obtained from fifty (15 per cent.) of the 332 patients as against nine (2·2 per cent.) of 400 patients suffering from uncomplicated NGU acting as controls. In thirty of the patients with Reiter's syndrome the family history was incomplete.

Discussion

Reiter's syndrome does not occur very frequently. An idea of its incidence can be formed from the Ministry of Health returns from the venereal clinics in England and Wales; the average of the annual figures for 1963 to 1967 was 333 cases, which represents just over 1 per cent. of all patients attending with NGU during this period. It is considered that six instances of multiple cases of Reiter's syndrome involving twelve patients in a consecutive series of 332 patients is more than would have been expected to have occurred by chance alone; moreover this number is probably too low, as not all the patients were able or willing to give full information about their families and sexual contacts. The multiple cases here described fall into two groups:

(1) Familial cases, represented by the two sets of brothers.

(2) Non-familial cases, to which the remaining eight patients belong.

Our familial cases as well as those reported by Morton (1958) showed several characteristics. A common sexually infectious source was absent, the family history for other rheumatic diseases, especially rheumatoid arthritis, was marked and the patients within each family showed a striking similarity in the clinical picture and course of the disease which was fairly severe. These features were not found in the non-familial cases. The evidence suggests strongly that the familial cases reported here were genetically determined.

The factor or factors responsible for the apparently very rare aggregation of Reiter's syndrome whether familial or not are unknown, but some of the possibilities which may act singly or in combination are:

(*i*) Specific infective aetiological agents.
(*ii*) Hereditary predisposition.
(*iii*) Abnormal qualitative or quantitative immune response.

A negative factor was suggested by several writers who believed that an infected prostate was the focus from which Reiter's syndrome and possibly ankylosing spondylitis were triggered off (Romanus, 1953; Mason, Murray, Oates, and Young, 1958). This idea was supported by the absence from earlier reports of cases in women of venereally transmitted Reiter's syndrome. However, it is now abundantly clear that women do get sexually transmitted Reiter's syndrome as shown by Oates and Csonka (1959) and various other authors, and as shown in the present series. This anatomically based factor can have only a limited validity and it is quite possible that the sexual distribution of Reiter's syndrome also has a genetic basis. Whatever the reason for lessened susceptibility of women to venereal Reiter's syndrome, it is reflected in the literature on multiple venereal cases which is almost entirely confined to those in male patients. In the present series three of the total of fourteen women seen developed their attacks in association with Reiter's syndrome in their consorts, and this is worth bearing in mind when investigating women with this illness. In two of the women, symptoms like those of rheumatoid arthritis were present in the absence of the rheumatoid factor, but the total clinical picture made a diagnosis of Reiter's syndrome very probable.

In the largest of the published series, that of 344 cases of post-dysenteric Reiter's syndrome, Paronen (1948) estimated that only 0·2 per cent. of those with dysentery developed the syndrome but that 10 per cent. occurred as multiple cases in families, and he commented that this was in excess of what was expected by chance; he also recorded that 10 to 14 per cent. of his patients gave a family history of rheumatoid arthritis or rheumatic fever but drew no conclusions from this. Allowing for the differences in epidemiology of the two precipitating infections, dysentery being likely to affect several members of a family whereas NGU is not, the figures noted by Paronen agree well with the relevant data in the present series.

Finally, the significantly higher incidence of rheumatoid arthritis in the families of our patients with Reiter's syndrome compared with that in the

controls adds to the evidence that genetic susceptibility plays a part in the development of this condition.

Summary

A series of 332 consecutive patients with Reiter's syndrome (318 men and 14 women) was investigated for the occurrence of multiple cases. Six instances involving twelve patients (9 men and 3 women) were found, and these included both familial and non-familial cases. The histories of these patients are briefly described and the significance of these observations is discussed.

A family history of rheumatoid arthritis was markedly more frequent in our cases of Reiter's syndrome than in a matched group of cases with uncomplicated non-gonococcal urethritis. This finding supports the view that genetic factors play a part in the development of Reiter's syndrome.

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Des cas multiples du syndrome de Reiter

RÉSUMÉ

Une série de 332 malades consécutifs atteints du syndrome de Reiter (318 hommes et 14 femmes) a été étudiée afin de chercher les cas multiples. Six exemples comprenant douze malades (9 hommes et 3 femmes) ont été trouvés, qui comprenaient des cas familiaux et non-familiaux. L'historique de ces malades est décrite brièvement et la signification de ces observations est discutée.

Un historique familial d'arthrite rhumatoïde était bien plus fréquent chez nos cas de syndrome de Reiter que dans un groupe de cas d'urétrite non-gonococcique sans complications. Cette observation soutient l'idée que les facteurs génétiques jouent un rôle dans le développement du syndrome de Reiter.